# Synthesis of Organic Carbamates without Using Phosgene: Carbonylation of Amines with Carbonic Acid Diesters

M. Carafa[1] and E. Quaranta[1,2,*]

[1]*Dipartimento di Chimica, Università di Bari, Campus Universitario, 70126, Bari, Italy*

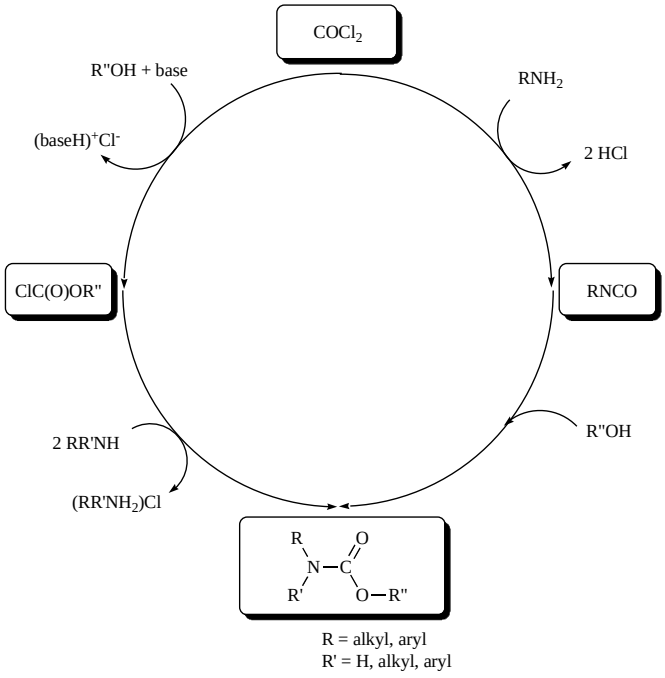
[2] *ICCOM-CNR, Dipartimento di Chimica, Campus Universitario, 70126, Bari, Italy*

**Abstract:** Aminolysis of organic carbonates is a suitable phosgene-free synthetic route to carbamate esters. The paper reviews recent advances in this field. Emphasis is laid on the reaction of amines with industrially relevant carbonic acid diesters, $(MeO)_2CO$, $(PhO)_2CO$, MeOC(O)OPh, currently obtainable without using phosgene. The carbonylation process may require a catalyst. The use of effective catalytic systems is highlighted and their mode of action is discussed.

**Keywords:** Carbamates, organic carbonates, phosgene substitution, carbonylation, catalysis.

## 1. INTRODUCTION

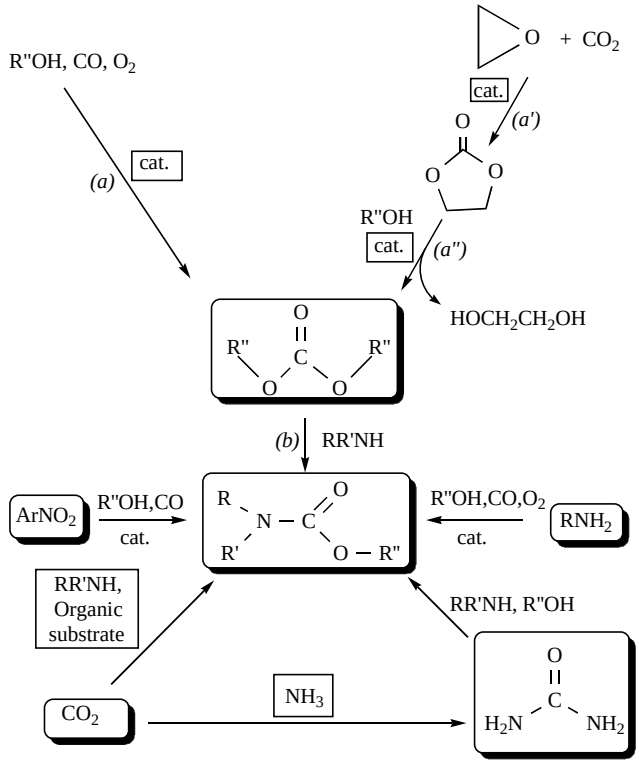
Carbamate esters [1] are very useful products. The carbamic functionality characterizes the molecular structure of several compounds which find application as pharmaceuticals [2] or agrochemicals [3]. Organic carbamates also play a key role in synthetic chemistry as suitable intermediates for protection of amino-group or as precursors of ureas, isocyanates, and polyurethanes [4]. The most common methods of synthesis of carbamate esters start from phosgene [1,5] and are based on either alcoholysis of phosgene, followed by aminolysis of intermediate choroformate, or the reaction of an alcohol with an isocyanate, usually prepared from $COCl_2$ (Scheme **1**).




**Scheme 1.** Conventional routes to carbamate esters.

Phosgene is notoriously a very risky compound [6]. Several environmental risks are implicit in the manufacture and use of this substance and include worker safety, corrosion of plants, waste disposal. Transportation and storage of phosgene also pose additional problems. Due to worldwide awareness of environmental hazards of phosgene and governmental policies for environment protection, many efforts are currently being focussed on replacing $COCl_2$ in organic synthesis with less noxious feedstocks [7-13]. Nevertheless, nowadays worldwide phosgene production ranges around 5-6 Mton/y, as this species is still used in chemical industry as a starting material for the synthesis of many other chemicals, besides carbamates, such as isocyanates, ureas, peptides, carbonates and polycarbonates [5].

The development of phosgene-free routes to carbamates is an important synthetic challenge and several synthetic strategies are currently under study (Scheme **2**). A few of them imply the carbonylation of nitroaromatic substrates [14], or the oxidative carbonylation of amines [15], or are based on the direct [8, 12, 16] or indirect, through urea [17], use of $CO_2$.




**Scheme 2.** Phosgene-free routes to carbamate esters.

The reaction of carbonic acid diesters with amines (eq. **1**) is another potential eco-friendly tool in the hands of chemists for the synthesis of organic carbamates (Scheme **2**).

$$RR'NH + (R"O)_2CO \longrightarrow RR'NC(O)OR" + R"OH \quad \textbf{(1)}$$

(R, R'= H, alkyl, aryl; R"= alkyl, aryl)

*Address correspondence to this author at the Dipartimento di Chimica, Università di Bari, Campus Universitario, 70126, Bari, Italy; Tel: 0039 080 5442100; Fax: 0039 080 5442129; E-mail: quaranta@chimica.uniba.it

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In this reaction an organic carbonate is used as "carbonyl" source instead of $COCl_2$ or toxic and hazardous phosgene-derivatives such as choroformates and isocyanates. The process also avoids any co-generation of chlorine-containing wasted salts, which are corrosive for industrial plants and need further treatment for their disposal. The sole co-product is alcohol, R"OH (eq. **1**), which, in principle, can be recovered and reused for the synthesis of the starting organic carbonate (see below).

In 1845 Cahours first reported the synthesis of ethyl urethane from ammonia and diethyl carbonate (DEC) [18]. Nevertheless, in the past, reaction **1** has drawn limited attention, as, for a long time, the most important synthetic way to organic carbonates was based on phosgene as the source of the carbonyl group (eq. **2a - 2b**) [5]

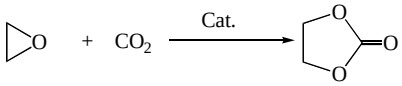
$$COCl_2 + ROH \xrightarrow{\text{Base}} ClC(O)OR + HCl \quad \textbf{(2a)}$$

$$ClC(O)OR + ROH \xrightarrow{\text{Base}} (RO)_2C(O) + HCl \quad \textbf{(2b)}$$

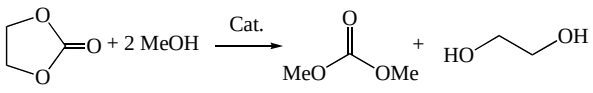
and, therefore, the conventional phosgene-based routes to carbamates (Scheme **1**) were, intrinsically, more direct and advantageous. Practical applications of reaction **1** have been limited to the reaction of amines with asymmetric organic carbonates having fairly good leaving groups, as 2-pyridyloxy- [19a,b], 8-chinolinyloxy- [19a], 6-(trifluoro-methyl)benzotriazolyl-1-oxy- [19c], 1-oxy-piperidine [19a], *N*-oxysuccinimide [19a,d-g], *N*-oxyphtalimide [19a], 4-oxy-3-oxo-2,5-diphenyl-2,3-dihydro-thiophen-1,1-dioxide [19a] or phenoxy groups containing electron withdrawing substituents (4-nitro- [19a,h-m], 2-nitro- [19a,n], 2,4-dinitro- [19a], 2,3,5-trichloro- [19a], 2,4,6-trichloro- [19a], pentachloro-[19a,o] , 4-acetyl- [19a]), which has been often proposed as alternative method of synthesis of carbamates in those cases wherein the conventional methods based on chloroformates or isocyanates were less or not practicable. The research activity in this area has brought to the development of very active substrates, such as alkyl 1-chloroalkyl carbonates [20a-c] or asymmetric α-methoxyvinylcarbonates ($H_2C$=C(OMe)OC(O)OR, $H_2C$=C(OMe)OC(O)OAr) [20d-f]. Unfortunately, the methods of synthesis of these "active carbonates" often use phosgene or chloroformates or are based on hazardous $COCl_2$-substitutes as triphosgene [5b,c].

In the last few years, innovative phosgene-free methodologies for the industrial synthesis of organic carbonates have been implemented. Both oxidative carbonylation of methanol (eq. **3**) [21] and oxirane carboxylation (eq. **4**) followed by methanolysis of intermediate cyclic carbonate (eq. **5**) [22] have been shown to be suitable routes for the industrial synthesis of dimethyl carbonate (DMC). Nowadays, several other organic carbonates, such as, for instance, methyl phenyl carbonate (MPC), diphenyl carbonate (DPC), diallyl carbonate, can be prepared, even on industrial scale, from DMC through transesterification processes (eq. **6** and **7**) [21c-d].

$$2\ MeOH + CO + \tfrac{1}{2}\ O_2 \xrightarrow{\text{Cat.}} (MeO)_2CO + H_2O \quad \textbf{(3)}$$



**(4)**



**(5)**

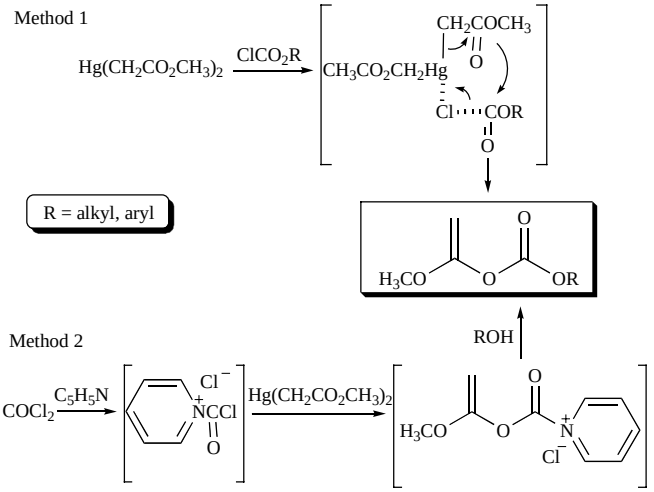
$$(MeO)_2CO + PhOH \xrightarrow{\text{Cat.}} MeOC(O)OPh + MeOH \quad \textbf{(6)}$$

$$2\ MeOC(O)OPh \xrightarrow{\text{Cat.}} (MeO)_2CO + (PhO)_2CO \quad \textbf{(7)}$$

The recent availability of these new routes to organic carbonates, as well as the current widespread attention to search for and develop greener and safer processes, have raised markedly the interest of both academia and industry for the synthesis of carbamates from amines and *unactivated* carbonates, as documented by the significantly growing number of relevant patents and scientific articles in the field. Scheme **2** shows clearly that, as a whole, both the routes *(a)* → *(b)* and *(a')* → *(a")* → *(b)* offer new solutions to the synthesis of carbamates without phosgene or phosgene derivatives. In this paper we focus on step *(b)* (Scheme **2**), which is shared by both the synthetic approaches: an overview on this research area is presented and the recent advances in the field are reviewed.

## 2. AMINOLYSIS OF ORGANIC CARBONATES: A GENERAL SURVEY

In general, asymmetric "active carbonates" (see above) react smoothly with basic amines [19]. Often, an auxiliary base, acting as proton scavenger, may be required. Tamura developed the synthesis of asymmetric α-methoxyvinylcarbonates (see Introduction), which easily reacted, under mild conditions, with aliphatic and aromatic amines to give carbamates [20d-f]. The starting carbonates were prepared from bis[(carbomethoxy)methyl]mercury and alkyl- or aryl-chloroformates or, in other cases, by using phosgene (Scheme **3**).




**Scheme 3.** Synthesis of α-methoxyvinylcarbonates.

Also diphenyl carbonate and methyl phenyl carbonate can react easily (293 K), in the absence of any catalyst, with aliphatic amines (benzylamine, for instance) to give, respectively, *O*-phenyl or *O*-methyl carbamates in high yield [23, 24].

Baba et al. have reported the high yield conversion of aliphatic diamines (1,6-diaminohexane, *m*-xylylenediamine, 1,3-cyclohexanebis(methylamine) and 5-amino-1-(aminomethyl)-1,3,3-trimethylcyclohexane) into the corresponding dimethoxycarbonyl derivatives by reaction with MPC, under mild conditions (323-363 K), in the absence of any catalyst [25]. The dicarbamate products are precursors of industrially important diisocyanates.

At ambient temperature, in $CH_2Cl_2$ or DMF as solvent, alkyl phenyl carbonates ROC(O)OPh (R = benzyl, *t*-butyl, allyl) smoothly reacted with several aliphatic polyamines in the absence of any catalyst [26]. The reaction has been exploited for developing a versatile direct method for selective Boc, Cbz and Alloc protection of primary amino groups in the presence of secondary ones (as in the cases of spermidine, spermine, diethylenetriamine, dipropylenetriamine), or for mono-carbamate protection of simple symmetrical aliphatic α,ω-alkanediamines. The method allows also to protect selectively a primary amino-group located on a primary carbon in the presence of a $NH_2$-group bound to a secondary or a tertiary

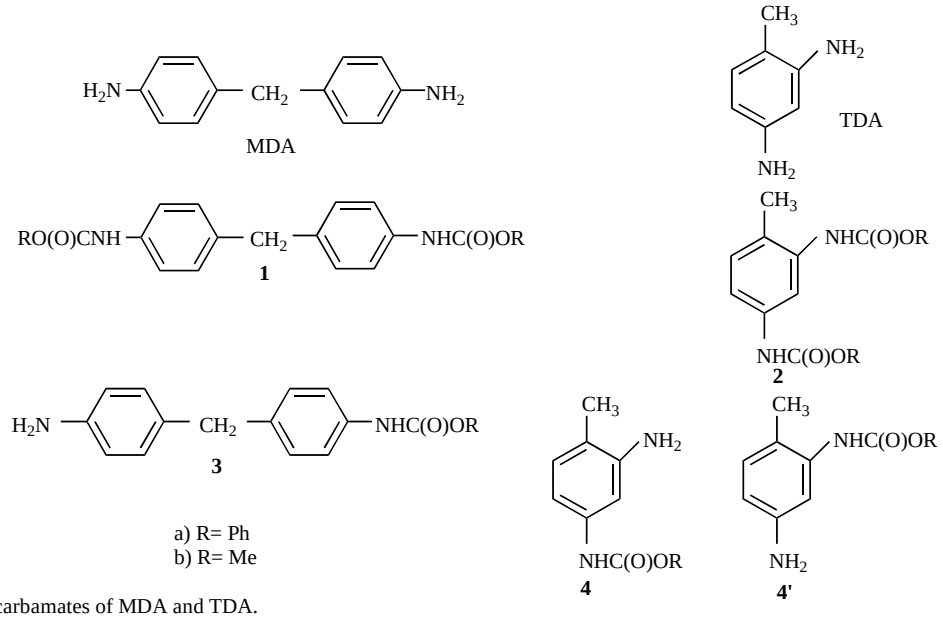



**Chart 1.** Mono- and dicarbamates of MDA and TDA.

carbon, as observed with 1,2-diaminopropane and 2-methyl-1,2-diaminopropane, respectively.

Aromatic amines are less reactive than the aliphatic ones. For instance, at 363 K, aniline reacted with DPC to give PhNHC(O)OPh in very low yield (< 3 % after 5 days) [23a]. In the temperature range 363-453 K, aromatic mono- and diamines, such as aniline, 4,4'-methylenedianiline (MDA) and 2,4-diaminotoluene (TDA) (Chart **1**), were not reactive towards MPC [25, 27].

In comparison with DPC or the alkyl phenyl carbonates considered above (MPC, ROC(O)OPh), unactivated dialkyl carbonates $(R"O)_2CO$ (DMC, DEC, for instance) exhibit an even poorer reactivity. In general, the reaction of poorly basic amines with DPC, MPC or other alkyl phenyl carbonates, as well as the reaction of dialkyl carbonates $(R"O)_2CO$ with aliphatic or aromatic amines, for the synthesis of carbamate esters, needs a suitable catalyst in order to observe an acceptable conversion rate. Moreover, high selectivity towards carbamation requires an accurate control of experimental conditions. In fact, depending on the working conditions (catalyst, temperature, etc), these reactions may afford also ureas and/or *N*-alkylation products. The search for effective catalysts with high selectivity to carbamation is a very challenging task.

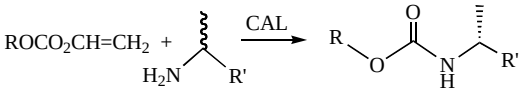
Most of studies in this area have dealt with DMC [21]. DMC is much less reactive than phosgene. In order to exhibit significant reactivity, it needs a much higher energy input than $COCl_2$. However, this drawback, which, often, can be overcome by using suitable catalysts, is largely compensated by several environmentally relevant advantages. DMC, in fact, is a non-toxic, easily biodegradable compound, which can be handled safely, without any particular caution. It exhibits a versatile reactivity as ambident electrophile and is currently under study not only as carbonylating agent succedaneous for toxic phosgene, but also as methylating substrate in place of poisonous and mutagenic methyl halides and dimethyl sulfate [28].

## 3. CARBONYLATION OF AMINES WHITH UNACTIVATED CARBONIC ACID DIESTERS: CATALYTIC PROCESSES

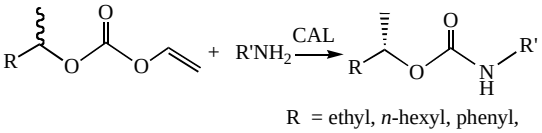
Different catalytic systems have been explored so far, which reveal different strategies adopted for activating the reactants (amine or organic carbonate). They include enzymatic systems [29], ionic liquids [30], organic and inorganic bases [31], Broensted acids [23a, b, 27, 33], metal-salts, -oxides, -complexes [24, 40-46] and, even, carbon dioxide [36, 38, 39].

### 3.1. Biocatalysts [29]

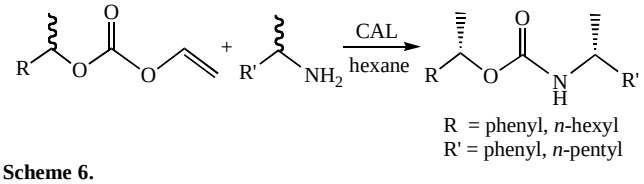
Gotor first reported the enzymatic alkoxycarbonylation of *n*-butyl amine with alkyl vinyl carbonates by using *Candida Antartica* lipases (CAL) as biocatalysts in organic solvents (diisopropyl ether), at ambient temperature [29a]. The method was further developed to obtain chiral carbamates from racemic amines under mild conditions (Scheme **4**) and allowed the kinetic resolution of racemic amines. The lipase, in fact, was enantioselective towards the *R* enantiomer. With a convenient combination of long-medium length of the amine and carbonate alkyl chains high e.e.'s (81-98 %, *R*) were achieved [29b]. Remarkably, when racemic vinyl carbonates were used, the enzyme was enantioselective (e.e.'s: 70-98 %) towards the *S* enantiomer (Scheme **5**) [29c]. As an extension of these studies, CAL was successfully used as biocatalyst for double enantioselective alkoxycarbonylation of racemic amines with racemic vinyl carbonates to yield, in one-step procedure, carbamates with two stereogenic centers (Scheme **6**) [29d].




**Scheme 4.**

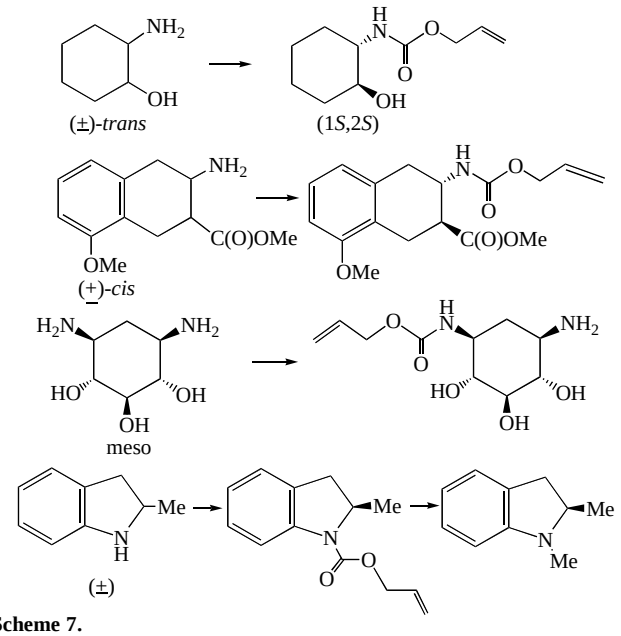



**Scheme 5.**

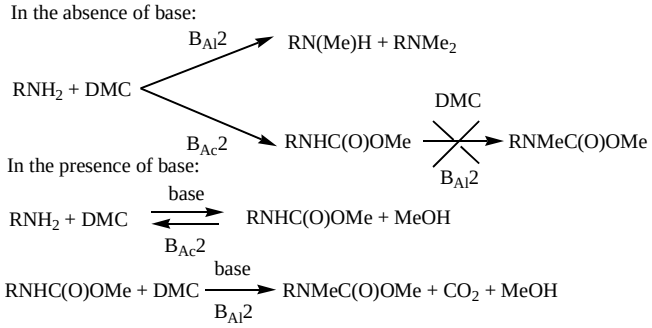



**Scheme 6.**

The activities of proteases and a few other lipases, with different origins, immobilized or not, have been also studied [29e,g]. Moreover, commercially available homo-carbonates $(RO)_2CO$ (R = Me, Et, allyl, *t*-butyl, benzyl) have been used in place of less readily available vinyl carbonates [29e,f,h].



**Scheme 7.**



**Scheme 8.** Reactivity of amines with DMC in the presence of bases (alkali alkoxides, alkali carbonates).

Using subtilisin BPN' as biocatalyst, diallyl carbonate has been successfully employed for allyloxycarbonylation of a few primary and secondary amines. Carbamation of the substrates reported in Scheme **7** took place with high chemo- and/or enantioselectivity. Carbamate product was subsequently deprotected or converted into the *N*-methyl derivative by reaction with $LiAlH_4$, providing a new procedure for the chemoenzymatic methylation of amines.

In a very recent work [29h], combined Ru and enzyme (*Candida Antarctica* lipase B) catalysis has been shown to be effective for chemo-enzymatic dynamic kinetic resolution of primary amines RR'CHNH$_2$ (R = Me; R' = Ph, *p*-Br-Ph, *p*-F-Ph, *p*-MeO-Ph, Cy, *n*-heptyl, *i*-propyl, $C_{10}H_{11}$) using dibenzyl carbonate as the acyl donor. Through this way benzyl carbamates have been obtained in high yield and high e.e. (> 90 %) and have been further deprotected, under very mild conditions, to give the free amine.

### 3.2. Ionic Liquids [30]

The utilization of ionic liquids (ILs) as catalysts for reaction **1** has been poorly explored so far. Deng and coworkers [30a] have reported that ILs, such as BMImX (BMIm = 1-butyl-3-methyl imidazolium; X = Cl, $BF_4$, $PF_6$, $HSO_4$), $BuPyBF_4$ (BuPy = 1-butylpyridinium), $RMImBF_4$ (RMIm = 1-alkyl-3-methyl imidazolium; R = ethyl, butyl, cetyl, benzyl), can be used as solvents and catalysts for methoxycarbonylation of cyclohexylamine and other primary or secondary aliphatic amines with DMC. After 1h at 443 K, whichever IL was used, conversion of cyclohexylamine was practically quantitative, but selectivity to carbamate CyNHC(O) OMe was strongly affected by the nature of the used salt. For instance, carbamate selectivity for $BMImHSO_4$ (46.9%) was much lower than that exhibited by the other BMImX salts investigated (78.5-82.7 %). Analogous experiments carried out with $RMImBF_4$ ILs, having different cations (R = ethyl, butyl, cetyl, benzyl; M = methyl), showed that the nature of the alkyl group R affected the distribution of products: the higher the number of carbon atoms in the alkyl chain at the 1-position, the lower the carbamate selectivity. Accordingly, with the 1-cetyl salt, large amounts of *N*-methylation products were obtained and selectivity to CyNHC(O) OMe was only 23.3 %.

In a more recent work [30b], the same group has shown that, under less severe conditions (353 K), $-SO_3H$ functionalised ILs RMImOTf (R = $CH_2)_mSO_3H$, m = 2,4,6,8; OTf = triflate) were very effective catalysts (≈ 1 wt%) for dicarbamation of 1,6-diaminohexane. RMImOTf ionic liquids were particularly active also in the methoxycarbonylation of linear monoamines (ethyl-, *n*-butyl, *n*-dodecylamine), but not so efficient for carbamation of cycloalkyl mono- and diamines (cyclohexylamine, 5-amino-1-(aminomethyl)-1,3,3-trimethylcyclohexane, 4,4'-diaminodicyclo-hexylmethane). The catalytic system was stable, easily separable and reusable. Unfortunately, it was completely inactive for carbamation of aromatic amines (aniline).

### 3.3. Base Catalysts [31]

A variety of base catalysts has been investigated so far. Amine itself may act as catalyst as suggested by the fact that *N*-alkyl carbamates have been claimed to be prepared also by treating aliphatic amines $RNH_2$ with DMC or DEC in the presence of excess of amine [31j].

A few early studies have dealt with the use of heterocyclic tertiary amines as catalysts for phenoxycarbonylation of aromatic amines with DPC [31g,h]. Such a process could not be promoted by monofunctional systems like pyridine, but bifunctional catalysts, such as 2-hydroxypyridine or imidazole, were effective in promoting the formation of PhNHC(O)OPh from aniline and DPC. At 333 K, the carbamation process was very selective (100 %), but high conversions to carbamate required long reaction times, even in the presence of stoichiometric amounts of base catalyst. The process was faster at higher temperatures (353-383 K), but also less selective because of formation of diphenylurea. The protocol was applied to the synthesis of diphenyl *N,N'*-arylene biscarbamates, which were prepared in high yield by reaction of DPC (2 equiv) with aromatic diamines (1 equiv) in the presence of 2-hydroxypyridine (1 equiv), but TDA gave poor results. More recently, *N*-heterocycles (2-hydroxypyridine, imidazole) have been claimed as active catalysts also for carbonylation of primary or secondary arylamines with aryl alkyl carbonates (MPC, for instance) for the synthesis of alkyl *N*-arylcarbamates [31i].

Different types of organic bases, such as alkali alkoxides [31a-f] or amidine and guanidine bases [31t,u], have been investigated as catalysts for alkoxycarbonylation of aliphatic or aromatic amines with dialkyl carbonates. In the presence of MOR (M = Na, K; R = alkyl) aliphatic mono- and diamines can be carbonylated with high yield under mild conditions [31d,e]. However, alkali alkoxides cannot be reused after reaction, as they have to be neutralized with production of wasted salts. With the view to overcoming this drawback the use of strongly basic ionic exchange resins has been explored [31g]. For instance, a mixture of 1,6-diaminohexane, DMC and Amberlyst A 27 was treated at 328 K for 8 h to give 1,6-dimethoxycarbonylaminohexane in 41.2% yield. According to another strategy, hybrid heterogeneous catalysts, prepared by anchoring organic bases on an inorganic material, have been emploied. TBD (1,5,7-triazabicyclo[4.4.0]dec-ene) immobilized on mesoporous MCM-41 silica was shown to be an efficient catalyst for the synthesis of carbamates by reaction of DEC with aliphatic amines [31u]. The products were generally obtained in good yields (52-98

%) and high selectivity (86-99 %) in 15 h, at 398 K. The hybrid solid catalyst can be recovered easily by filtration and reused for different cycles without apparent loss of activity.

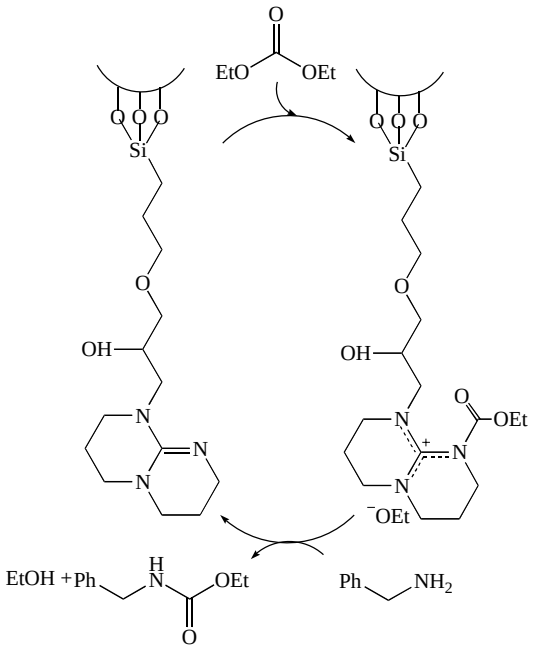
Very recently the activities of a few base organocatalysts, TBD, (4-*N*,*N*-dimethylamino)pyridine (DMAP), *N*-methylimidazole (*N*-Mim), L-proline, have been compared in the reaction of TDA with DMC, in the range 378-398 K, using different DMC/TDA molar ratios (30 and 10 mol/mol, respectively) and a catalyst load equal to 10 mol % *vs* TDA [31v]. While L-proline was practically inactive, the other catalysts exhibited low (TBD) to moderate (DMAP, *N*-Mim) activity, which increased with reaction temperature. Generally, *N*-methylation was the predominant process, but variable proportions of *N*-carbonylation were also observed. Reaction kinetics indicated that *N*-methylation and *N*-methoxycarbonylation were independent and parallel processes. The *N*-methylation/*N*-methoxycarbonylation ratio was influenced by the reaction conditions (organocatalyst used, DMC/TDA molar ratio, temperature).

Alkoxycarbonylation can be assisted or catalyzed also by inorganic bases such as NaH [31w] or alkali carbonates. Lissel et al. reported that aniline can be methoxycarbonylated with DMC in the presence of $K_2CO_3$ and 18-crown-6-ether [31l,m]. A facile synthesis of *N*-methyl-*N*-aryl carbamates from aromatic amines and DMC has been achieved using $K_2CO_3$ and a phase transfer catalyst ($Bu_4NBr$) as the catalytic system [31n]. $K_2CO_3$ was also an effective catalyst for carbonylation of *o*-aminophenol. At 403-423 K, in the presence of $K_2CO_3$, *o*-aminophenol reacted with dialkylcarbonates $(RO)_2C=O$ (R = Me, Et, allyl, benzyl) to give the corresponding *N*-alkylbenzoxazol-2-ones [31o]. In this reaction the dialkyl carbonate behaves as carbonylating and alkylating agent. The analogous reaction with *p*-aminophenol was completely unselective. In the presence of $K_2CO_3$ as a catalyst, the reaction of *p*-aminophenol with DMC produced a great variety of products, which formed through several competitive *O*- and *N*-methylation and methoxycarbonylation processes. Remarkably, switching to NaY faujasite catalysts changed drastically the chemoselectivity of the reacting system. In the presence of NaY zeolites both *o*- and *p*-aminophenol reacted with DMC in a very selective way with formation of the mono-*N*-methylated products which were isolated in high yield (91-99 %) [28d].

To date, the use of supported solid base catalysts has attracted poor attention. Recently, MgO supported on $ZrO_2$ was found to be a moderately active catalyst, at 363 K, for dicarbamation of 1,6-diaminohexane with DMC. Remarkably, carbamate yield over $MgO/ZrO_2$ (6 wt%) was significantly higher (max. 53.1 %) than that over MgO or $ZrO_2$, as a result of the fact that MgO loading on $ZrO_2$ allowed to achieve higher basicity than that exhibited by MgO or $ZrO_2$ [31p].

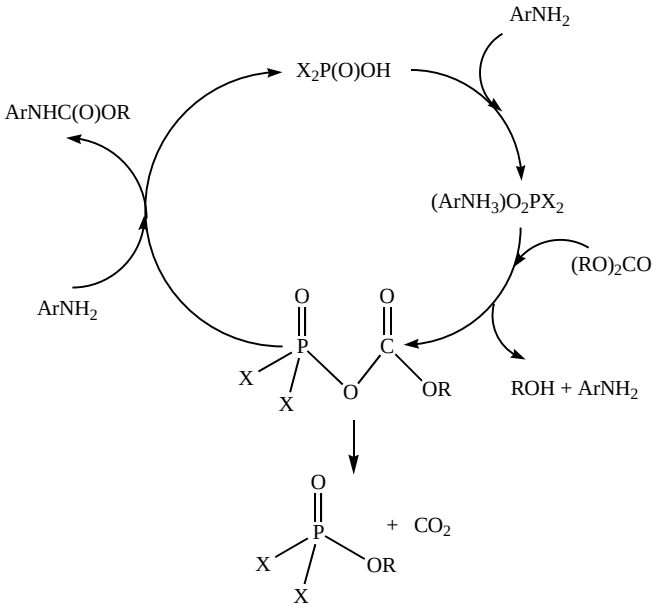
The reactivity of amines with DMC in the presence of bases, like alkali alkoxides or carbonates, has been matter of a few mechanistic studies [31q-s]. It has been proposed that *N*-methylation and *N*-methoxycarbonylation proceed through $B_{Al}2$ and $B_{Ac}2$ mechanisms, respectively. In the absence of any catalyst, both processes take place with poor yield and selectivity (Scheme **8**). In the presence of the aforementioned bases, the $B_{Ac}2$ mechanism prevails. Carbamate RNHC(O)OMe, once formed, can undergo *N*-methylation by reaction with DMC, *via* $B_{Al}2$ mechanism, to give the corresponding *N*-methyl derivative (Scheme **8**).

It is generally assumed that the base may enhance the nucleophilicity of the attacking species (amine or carbamate RNHC(O)OMe) and activate it by increasing the negative charge on the N-atom through the formation of a hydrogen bridge RR'N---H---B (R = alkyl, aryl; R' = -H, -C(O)OMe; B = base) or the formation of an anionic species $RR'N^-$ [31r,v]. The pronounced double selectivity ($B_{Ac}2/B_{Al}2$) which characterizes, under proper conditions (prolonged reaction times; absence of $CO_2$), the selective formation of *N*-methyl carbamate RNMeC(O)OMe has been rationalized according to the Pearson's Hard and Soft Acid-Base (HSAB) theory [31q,r,32]. Very recently, the HSAB formalism has been applied also to explain the distribution of the products observed in the base (alkali alkoxides or carbonates) promoted reaction of DMC with an ambident nucleophile such as *N*-phenylhydrazine [31s].




**Scheme 9.** Proposed mechanism for the reaction of amines with DEC in the presence of TBD immobilized on MCM-41 silica.

A different mechanism seems to be operative with guanidine hybrid catalysts (Scheme **9**) [31u]. The mechanism proposed involves a nucleophilic catalysis by the guanidine base, which attacks DEC to give a *N*-carbethoxyguanidinium species as active intermediate, whose formation was supported by spectroscopic data. Control experiments have excluded that, under the working conditions, $EtO^-$ anion may play any important catalytic role in the carbamation process.




**Scheme 10.**

### 3.4. Broensted Acid Catalysts [23a,b,27,33]

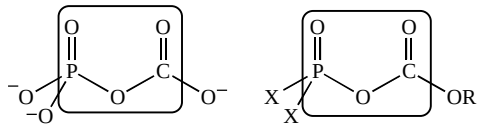
Several carboxylating enzymes (carbamoyl phosphate synthetase (CPS), biotin dependent carboxylases, phosphoenol pyruvate carboxylase) use poorly electrophilic bicarbonate anion, instead of $CO_2$, as the source of carbon and activate it through the intermediacy of carboxyphosphate mixed anhydride, $^-O_2COPO_3^{2-}$ (CP), resulting from the interaction of ATP with $HCO_3^-$ (eq. **8**) [34]. Remarkably, in natural systems, the reaction of CP with ammonia

$$ATP + HCO_3^- \xrightarrow{\text{enzyme}} ADP + {}^-O_2COPO_3^{2-} \quad \textbf{(8)}$$

(eq. **9**) generates carbamate anion, $H_2NCO_2^-$ [34b].

$$^-O_2COPO_3^{2-} + NH_3 \xrightarrow{\text{CPS}} H_2NCO_2^- + HOPO_3^{2-} \quad \textbf{(9)}$$

A few molecular systems, such as phospho-carbonic mixed anhydrides $X_2P(O)OC(O)OR$ (R = alkyl, aryl; X = alkyl, aryl, alkoxy, aryloxy), are closely related to CP not only structurally (Chart **2**),



CP phospho-carbonic mixed anhydride

**Chart 2.**

but also from the point of view of their reactivity. These compounds are readily prepared from sodium semi-carbonates $ROCO_2Na$ and organo-phosphorus acid chlorides $X_2P(O)Cl$ (eq. **10**) [23a], but, in general, exhibit modest stability because of their

$$ROCO_2Na + X_2P(O)Cl \longrightarrow X_2P(O)OC(O)OR + NaCl \quad \textbf{(10)}$$

tendency to rearrange intramolecularly by releasing $CO_2$ (eq. **11**), even at ambient temperature. The decarboxylation process is strongly accelerated by temperature.

$$X_2P(O)OC(O)OR \longrightarrow X_2P(O)OR + CO_2 \quad \textbf{(11)}$$

Likewise CP, $X_2P(O)OC(O)OR$ mixed anhydrides are very reactive species and can play a key role as intermediates in the synthesis of carbamate esters. In fact, they easily react with aliphatic and aromatic amines to give the corresponding carbamate (eq. **12**) in quantitative yield. At 293 K, reaction **12** takes place instantaneously and, even at 363 K (X = Ph, R = Me, R' = Ph), is much faster than the decarboxylation process (eq. **11**) [23a].

$$X_2P(O)OC(O)OR + 2\ R'NH_2 \longrightarrow R'NHC(O)OR + (R'NH_3)O_2PX_2 \quad \textbf{(12)}$$

Following the idea that the carbonyl group of carbonic acid diesters can be activated towards nucleophilic attack by amines through the intermediate formation of a phospho-carbonate $X_2P(O)OC(O)OR$ species, Aresta, Quaranta *et al.* developed a new synthetic strategy for building up carbamate moiety from aromatic amines and carbonates, which was based on the use of organo-phosphorous Broensted acid catalysts $X_2P(O)OH$ ($Ph_2P(O)OH$; $(PhO)_2P(O)OH$; commercial equimolar mixture of $(BuO)_2P(O)OH$ and $BuOP(O)(OH)_2$) under not severe conditions (323-393 K) [23a,b,27,33b].

An interesting catalytic activity was shown by $Ph_2P(O)OH$. For instance, at 393 K, in THF as solvent, PhNHC(O)OPh was obtained in high yield (98 %) and selectivity (≥ 99 %) by reacting DPC with aniline (DPC/$PhNH_2$ = 2.7 mol/mol) in the presence of $Ph_2P(O)OH$ (6.3 mol % *vs* $PhNH_2$) for 15 h.

The process was successfully extended to the phenoxycarbonylation of other mono-amines, as 1-aminonaphtalene [23a], and bis-carbamation of industrially relevant aromatic diamines, such as MDA and TDA [23b]. High yield (> 90%) conversions of MDA and TDA into the corresponding bis-phenyl carbamates (**1a**) and (**2a**) (Chart **1**) were achieved at 363 K, by using DPC both as reagent and reaction medium. Under these conditions the carbamation reaction was very selective and no formation of ureas was observed. Through an accurate choice of experimental conditions (temperature, solvent, catalyst, reaction time), the process was addressed also to the selective formation of monocarbamates (**3a**) and (**4a**).

Other carbonates, such as DMC [23a] and MPC [27], were also used as carbonylating agents. The reactivity of carbonates diminished in the order DPC>MPC>DMC. MPC was a very selective methoxycarbonylating agent for MDA and TDA [27], as side-products, as *O*-phenyl carbamate esters or methylated amines or *N*-methyl carbamates, never formed under the used conditions.

Scheme **10** describes a plausible reaction pathway for the carbamation process. In the presence of amine, $X_2P(O)OH$ easily converted into the corresponding ammonium salt (eq. **13**), which was isolated and characterized. $(ArNH_3)O_2PX_2$ salt acted as the truly

$$X_2P(O)OH + ArNH_2 \rightleftharpoons (ArNH_3)O_2PX_2 \quad \textbf{(13)}$$

catalytically active species, as, if added in catalytic amount (1-10 mol %) to a mixture of the corresponding aromatic amine and organic carbonate (DPC, MPC, DMC), it promoted the carbamation process. A key role in this mechanism is believed to be played by the acid's conjugated base, $X_2PO_2^-$, which reacts with the organic carbonate to give a phospho-carbonic mixed anhydride, $X_2P(O)OC(O)OR$. This species, by reacting fast with the free amine (see above), converts into the carbamate ester and regenerates the acid catalyst. In accordance with the proposed mechanistic pathway, the better performance of $Ph_2P(O)OH$ with respect to the closely related $(PhO)_2P(O)OH$ was ascribed to the stronger nucleophilicity of $Ph_2PO_2^-$ with respect to $(PhO)_2PO_2^-$ anion, as the $pK_a$ values[1] for $Ph_2P(O)OH$ and $(PhO)_2P(O)OH$ suggest. Accordingly, under comparable conditions, other ammonium salts with a much poorer nucleophilic counteranion, such as $(ArNH_3)X$ (X = Cl, OTf), showed a negligible catalytic effect. Carboxylic acids [23a, 33], such as trifluoroacetic ($pK_a$ = 0.52) or propionic acid ($pK_a$ = 4.87) were less effective than the used $X_2P(O)OH$ acids. Remarkably, in the latter cases, the strongest acid ($CF_3C(O)OH$) exhibited also the highest catalytic activity [23a].[2]

The proposed mechanism easily accounted for the inhibitory effect due to alcohols or phenol, when these species were used as reaction solvents. Both PhOH and ROH, in fact, can compete with amine for the mixed anhydride $X_2P(O)OC(O)OR$, which reacts to give carbonate ROC(O)OR' (eq. **14**) instead of target carbamate.

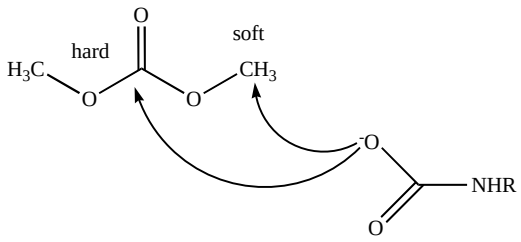
$$X_2P(O)OC(O)OR + R'OH \longrightarrow ROC(O)OR' + X_2P(O)OH \quad \textbf{(14)}$$

The catalyst worked for several hours and, depending on the carbonate used (DPC, MPC, DMC), may deactivate by converting into $X_2P(O)OMe$ (DMC, MPC) or $X_2P(O)OPh$ (DPC). Deactivation of catalyst was less important with DPC.

Also the formation of $X_2P(O)OR$ (R = Me, Ph) can find an easy rationale in the proposed mechanism (Scheme **10**), which emphasize the crucial role played by the mixed anhydride in the catalytic process. As reported above, this species may convert into the final product by reaction with amine (eq. **12**), but may also open the way to the deactivation of the catalyst (eq. **11**).

[1] The $pK_a$ of $Ph_2P(O)OH$ and $(PhO)_2P(O)OH$, measured in aqueous EtOH (75 %), were 4.70 and 2.78, respectively. The $pK_a$ of $Ph_2P(O)OH$ in $H_2O$ is equal to 1.74-1.76; the $pK_a$ of $(PhO)_2P(O)OH$ in $H_2O$ can be estimated to be close to 0.76, which is the value measured for $(MeO)_2P(O)OH$ ([23a] and references therein).

[2] Carboxylic acids are well known to catalyze the aminolysis of active esters through a bifunctional catalysis: the catalytic activity decreases with increasing the $pK_a$ of acid [35].




**Scheme 11.**

### 3.5. Carbon Dioxide as Catalyst [36]

The ability of $CO_2$ to accelerate the methoxycarbonylation of primary aliphatic amines with DMC was first documented by Aresta and Quaranta [36a,b]. Under $CO_2$, amine (benzyl-, allyl-, Cy-$NH_2$) carbamation proceeded faster than under a $N_2$ atmosphere and carbamate ester productivity was higher (45-92 %, in 24 h at 363 K). Selectivity to carbamate was also very high (≥ 97 %). Methylated amines (eq. **15** and **16**) formed in very low yield and other

$$RNH_2 + (MeO)_2CO \longrightarrow RN(Me)H + MeOH + CO_2 \quad \textbf{(15)}$$

$$R(Me)NH + (MeO)_2CO \longrightarrow RNMe_2 + MeOH + CO_2 \quad \textbf{(16)}$$

side-products, such as *N*-methyl carbamates RNMeC(O)OMe or ureas $(RNH)_2CO$, if any, were detected in trace amounts. The reaction conditions were mild (333-363 K; $CO_2$ pressure = 0.1 MPa) and DMC itself can be employed as reaction solvent. Recently, the use of supercritical $CO_2$, as reaction medium for the process [38, 39], has been explored by Selva [38] and by Tester and Danheiser [39].

Under $CO_2$, aliphatic primary amines $RNH_2$ (R = benzyl, allyl, cyclohexyl, etc) easily convert into the corresponding alkylammonium carbamate salts by reaction with the heterocumulene (eq. **17**) [16f, 36e]. The salt was formed *in situ* (DMC) at ambient tempera-

$$2\ RNH_2 + CO_2 \rightleftharpoons (RNH_3)O_2CNHR \quad \textbf{(17)}$$

ture and, once precipitated, allowed to react with the organic carbonate at the working temperature (333-363 K) to give the relevant carbamate ester (eq. **18**).

$$(RNH_3)O_2CNHR + (MeO)_2C{=}O \longrightarrow$$

$$RNHC(O)OMe + MeOH + CO_2 + RNH_2 \quad \textbf{(18)}$$

Fig. (**1**) shows the kinetics of formation of $PhCH_2NHC(O)OMe$ from benzylamine and DMC under $CO_2$ (curve (a)) and $N_2$ (curve (b)) atmosphere. Under $N_2$, a long induction time was observed. In the latter case (curve (b)), when the synthesis of carbamate began to take place at higher rate, alkylammonium carbamate was present in the reaction medium, as a result of the reaction of $PhCH_2NH_2$ with $CO_2$ generated according to eqs. **15** and **16**. Under $N_2$, the presence of a weak acid such as $PhCH_2NH_3^+$ (from $PhCH_2NH_3Cl$; curve (c)) shortened, but did not eliminate, the induction time. Therefore, the systems $DMC/RNH_2/N_2$ or $DMC/RNH_2/RNH_3^+/N_2$ were not so effective as the system $DMC/RNH_2/CO_2/(RNH_3)O_2CNHR$. These facts exclude that, under $CO_2$, formation of carbamate ester involves, as main reaction pathway, the ($RNH_3^+$ assisted or not) reaction of DMC with free amine present at the equilibrium (eq. **17**), and indicate that carbamate ester forms, prevailingly, by reaction of $(RNH_3)O_2CNHR$ salt with DMC (eq. **18** ).

DMC, as ambident electrophile, shows two acid sites for interacting with a nucleophile such as carbamate anion: a) the "soft" methyl carbon atoms; b) the "hard" carbonylic carbon (Scheme **11**). The reaction of $(RNH_3)O_2{}^{13}CNHR$ with DMC under $^{13}CO_2$ atmosphere gave unlabelled carbamate $RNH^{12}C(O)OMe$ [36b]. This result rules out that DMC in this process behaves as a methylating

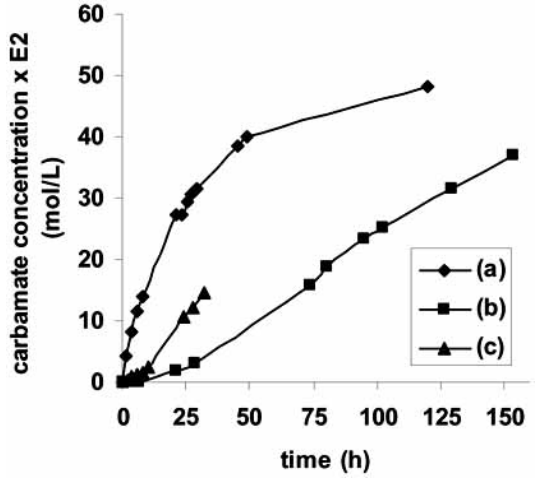
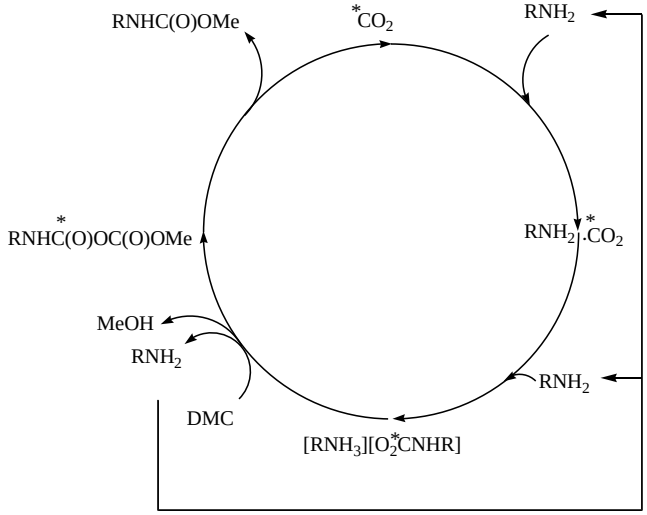
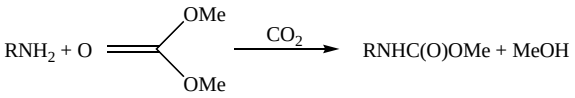



**Fig. (1).** Kinetics of RNHC(O)OMe (R = benzyl) formation from $RNH_2$ (18.3 mmol) and DMC (20 mL), at 343 K. (**a**) under $CO_2$ (0.1 MPa); (**b**) under $N_2$ (0.1 MPa); (**c**) under $N_2$ (0.1 MPa), in the presence of $RNH_3Cl$ (9.05 mmol).




Overall process:




**Scheme 12.**

agent of carbamate anion and is more easily explained taking into account the interaction between the carbonyl carbon of DMC and the O-end of carbamate ion (Scheme **11**) to give a carbamic-carbonic mixed anhydride (eq. **19**), which, by decarboxylation, converts into the target carbamate (eq. **20**). Mixed anhydrides RNHC(O)OC(O)OMe have been prepared by a different way (eq. **21**) and isolated at low temperature (233 K): these compounds

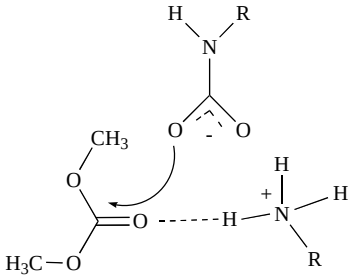
$$(RNH_3)O_2CNHR + (MeO)_2C{=}O \longrightarrow$$
$$RNHC(O)OC(O)OMe + MeOH + RNH_2 \quad \textbf{(19)}$$

$$RNHC(O)OC(O)OMe \longrightarrow RNHC(O)OMe + CO_2 \quad \textbf{(20)}$$

$$(RNH_3)O_2CNHR + ClC(O)OMe \longrightarrow$$
$$RNHC(O)OC(O)OMe + (RNH_3)Cl \quad \textbf{(21)}$$

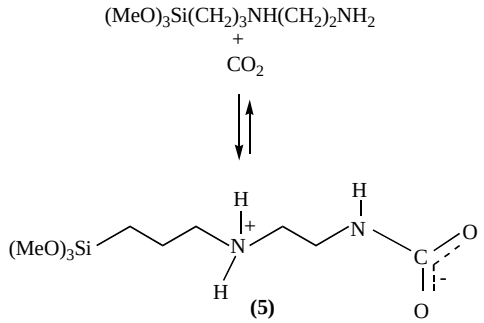
exhibit very modest stability as, even at ambient temperature (293 K), convert into the corresponding carbamate esters through very fast intramolecular decarboxylation (eq. **20**) [36b].

According to labelling experiments, $CO_2$ is selectively lost from the carbamic moiety of the mixed anhydride. Consequently, the $CO_2$ molecule initially fixed by the starting amine is not incorporated in the final product, but is released when the organic carbonate is formed. Scheme **12** clearly indicates that $CO_2$ plays the role of catalyst of the methoxycarbonylation process. The use of $CO_2$ as catalyst for reaction (**1**) (R' = H, R" = Me) is particularly attractive, as this species is inexpensive, non toxic and does not present regeneration and recycling problems.



**Scheme 13.**

The $CO_2$-promoted reaction of primary amines with DMC (eq. **1**; cat. = $CO_2$) has been investigated from a theoretical point of view [36d] according to the "Selective Energy Transfer (SET) model" [37]. The application of this model supported that the rate determining step of the overall process was the formation of the carbonic-carbamic mixed anhydride by reaction of the ion pair $RNH_3^+ \ ^-O_2CNHR$ with DMC (eq. **19**) [36d]. As the ion pair is approaching the organic carbonate, a hydrogen bond between the alkylammonium cation and the carbonyl oxygen of DMC is formed. The H-bond opens up a reactive pathway for the splitting off of a molecule of methanol and the simultaneous release of a molecule of the amine (Scheme **13**).



**Scheme 14.**

The synthetic methodology was extended to the carbamation, under mild conditions (343-348 K, $P_{CO2}$ = 0.1 MPa), of a few industrially relevant aminofunctional silanes, such as $H_2N(CH_2)_3Si(OMe)_3$, $H_2N(CH_2)_3Si(OEt)_3$, $H_2N(CH_2)_2NH(CH_2)_3Si(OMe)_3$ [36c].

$H_2N(CH_2)_2NH(CH_2)_3Si(OMe)_3$, which contains both a primary and a secondary amino-group, was selectively methoxycarbonylated at the primary one. In this case, the first step was the reaction of $CO_2$ with the diamine to afford zwitterion (**5**) (Scheme **14**), which was isolated and characterized [36c,e].

Amine $H_2NC(O)NH(CH_2)_2NH(CH_2)_3Si(OMe)_3$, which contains a secondary amino-group as well as ureidic $NH/NH_2$ groups, poorly reacted with $CO_2$ (0.1 MPa). Consequently, its reactivity with respect to carbamation was very modest and, under the working conditions used for the other aforementioned aminofunctional silanes, reacted with DMC to give only *N*-methylated products.

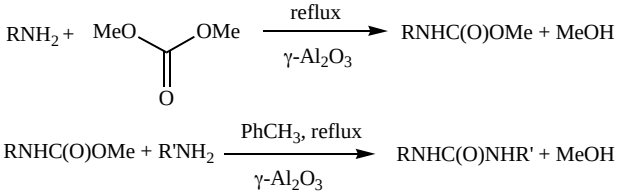
The latter results emphasize clearly how much sensitive is the methodology to the nature of amine substrate. Accordingly, this method was not suitable for methoxycarbonylation of aromatic amines, which do not react with $CO_2$ according to reaction (**17**) because of their lower basicity.

### 3.6. Metal Catalysts [24, 40-46]

To date, several metal systems, both homogeneous and heterogeneous, have been studied as catalysts for reaction (**1**). The catalytic systems investigated range from oxides to salts or complexes of several metal elements such as Ti [40j], Zr [45a], Hf [46b], Nb [40a], Mn [40e], Fe [40d], Co [40c], Ru [40d], Rh [40d], Ni [40i], Cu [40f], Zn [40c,d,f,42,43,44], Al [40d,41], In [45b], Tl [40g], Sn [40b-d,43a], Pb [44], Sb [40a], Bi [42,44c], U [40a], Sc[24,46b,e,f], Y [46c,b], La and RE (Rare Earth) elements [24, 46a-e]: the catalytic activity of most of them has been claimed in the great number of industrial patents delivered in this field.

In an early paper [40d], Porta *et al.* reported that, at 333 K, in the presence of metal compounds, such as $SnCl_2$, $AlCl_3$, $FeCl_3$, $ZnCl_2$, $Zn(O_2CCH_3)_2{\cdot}2H_2O$, $RuCl_3{\cdot}3H_2O$, $RhCl_3{\cdot}3H_2O$, $Ru(PPh_3)_2Cl_2$, $Rh(PPh_3)_3Cl$, the reaction of *n*-propylamine with diethyl carbonate (amine/DEC = 3:1 mol/mol) afforded ethyl *N*-propyl carbamate. $SnCl_2$, $AlCl_3$, $FeCl_3$ were among the most active catalysts. Under the conditions explored for *n*-propylamine, $AlCl_3$ or $FeCl_3$ were not active for ethoxycarbonylation of aniline [40d].

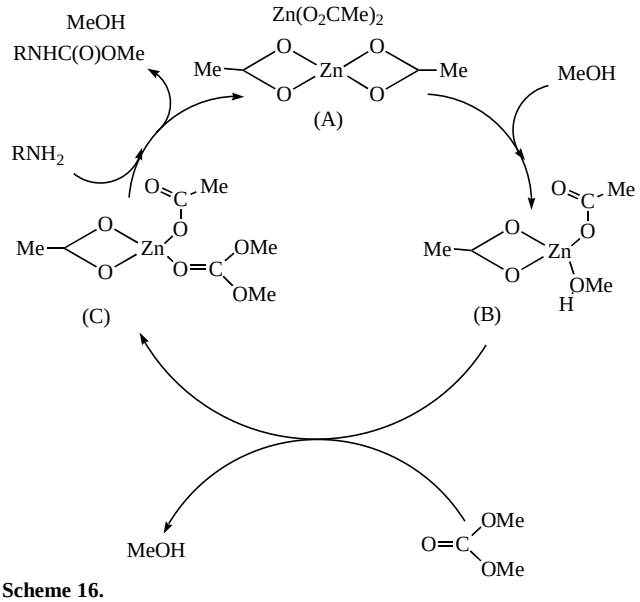
However, a few Al-based catalytic systems have been successfully used as alkoxycarbonylation catalysts of aromatic amines [41]. For instance, under reflux conditions, $\gamma$-$Al_2O_3$ was an active catalyst for methoxycarbonylation of aliphatic and aromatic amines (amine/alumina = 1:1 wt/wt) with DMC (amine concentration = 0.28 M) [41b]. $\gamma$-$Al_2O_3$ was also effective in promoting the conversion of carbamates into symmetrical and unsymmetrical ureas (Scheme **15**). Unfortunately, large amounts of alumina were required for both reactions. The use of lower amounts of catalyst caused a considerable increase of reaction time. Nevertheless, the catalyst is cheap, safe and can be reused after thermal activation.



**Scheme 15.**

The activity of zinc acetate as carbamation catalyst for aromatic amines has been studied in detail. Zinc acetate, which is moderately active in the alkoxycarbonylation of aliphatic mono- [40d] and diamines [42], is a much more effective catalyst for carbonylation of anilines [43]. Gurgiolo first claimed the catalytic activity of the salt in promoting the carbamation of aromatic amines with organic carbonates [43a]. More recently, Baba *et al.* have investigated the reaction of DMC with TDA and MDA in the presence of the zinc salt [43c,e]. At 453 K, the anhydrous salt, prepared by heating *in vacuo* $Zn(O_2CCH_3)_2{\cdot}2H_2O$ at 383 K for 2h, promoted the formation of (**2b**) from TDA and DMC in 96 % yield in 2 h. At the same temperature, the hydrate salt $Zn(O_2CCH_3)_2{\cdot}2H_2O$ catalyzed the bis-methoxycarbonylation of MDA with DMC as much well: after 2 h, the conversion into (**1b**) was as high as 98 %. Methanol, which is a reaction coproduct or may form under the working conditions by decomposition of DMC, can accelerate the carbamation process. The role of methanol was further investigated and a mechanism for DMC activation (Scheme **16**) has been proposed [43e]. According to the suggested mechanism, methanol is believed to induce a coordination change (bidentate to monodentate) of acetate ligand coor-

dinated to Zn(II) (species B, Scheme **16**). This facilitates the coordination of DMC to Zn(II) ion (species C) and the activation of the carbonyl group of the organic carbonate towards the nucleophilic attack by amine. The appearance of a band at 1722 $cm^{-1}$ in the IR spectrum of a $CHCl_3$ solution containing the organic carbonate (DMC), the salt ($Zn(O_2CCH_3)_2 \cdot 2H_2O$) and the alcohol (MeOH) was adduced as the experimental evidence in support of the formation of the DMC-Zn(II) adduct.




**Scheme 16.**

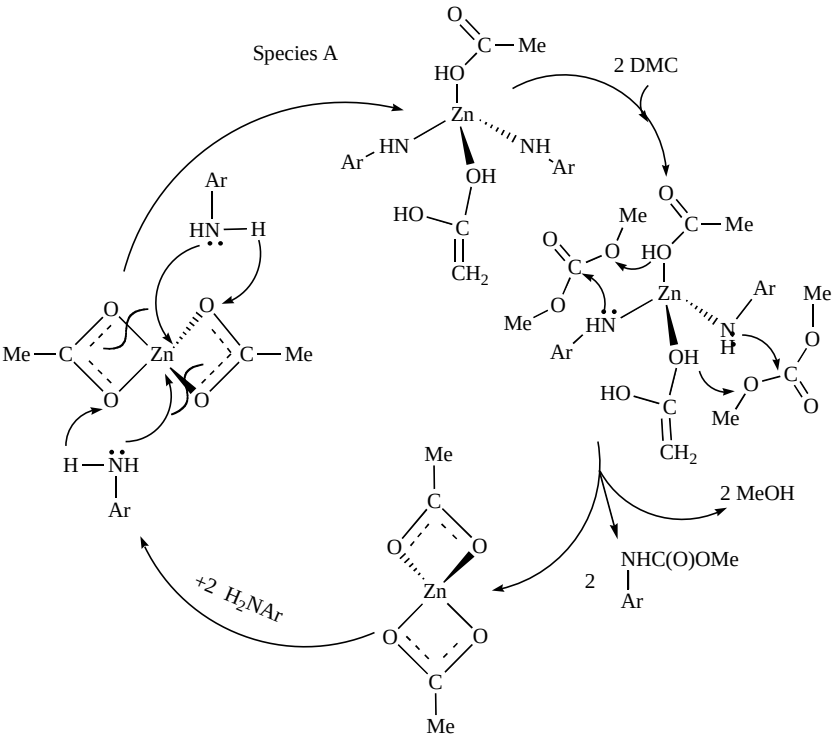
The final fate of the zinc catalyst has been recently investigated by Ma *et al.*, who used $Zn(O_2CCH_3)_2$ as catalyst for methoxycarbonylation of TDA with DMC [44d]. A XRD study [44d] on the catalyst recovered after reaction showed that $Zn(O_2CCH_3)_2$ converted, during the catalytic run, into ZnO, which is catalytically not active [43c]. Both methyl acetate and water were also detected in the reaction mixture, suggesting that $Zn(O_2CCH_3)_2$ reacted with methanol and converted into ZnO according to reaction **22** [44d].

$$Zn(O_2CCH_3)_2 + 2\ CH_3OH \longrightarrow ZnO + 2\ CH_3C(O)OCH_3 + H_2O \quad \textbf{(22)}$$

Zinc acetate, as well as other zinc salts of carboxylic acids, promoted, catalytically, also the methoxycarbonylation of 1,5-diaminonaphtalene (NDA) with DMC to 1,5-naphtalene dicarbamate (NDC). NDC yields as high as 95% were achieved [43f]. The reaction of NDA with DMC over anhydrous zinc acetate, at 443 K, has been recently investigated from a mechanistic point of view [43g]. Differently from NDA, which can coordinate to Zn(II), gaseous DMC hardly interacted with anhydrous zinc acetate in the temperature range 293-453 K. Consequently, a mechanism for the methoxycarbonylation of NDA has been proposed, which implies activation of diamine by the zinc salt (Scheme **17**), rather than activation of the organic carbonate [43g]. According to the proposed mechanism, activation of NDA by the metal centre modifies the coordination mode of acetate ligand to Zn and affords an intermediate (**A**) (Scheme **17**), which, on the basis of only FT-IR analyses, has been suggested to contain an enediol moiety mono-bound to the metal. The reaction of **A** (Scheme **17**) with DMC should afford the carbamate product.

Use of zinc acetate catalyst may cause troublesome problems in recovery of the catalyst and difficulties in purification of the products [43d]. In the attempt to overcome these drawbacks supported zinc acetate catalysts have been prepared and investigated for their methoxycarbonylating activity in the reaction of aromatic mono- and diamines with DMC [43d,h]. Unfortunately, these catalysts were less effective than unsupported zinc acetate. Moreover, the catalyst recovered after reaction showed a significantly reduced activity, because of serious leakage of zinc from support.

In principle, leakage of catalytic species from support may be prevented by using supported metal oxide catalysts [45]. Li *et al.* used $In_2O_3/SiO_2$ as catalyst, but the catalytic activity was low and methyl *N*-phenylcarbamate yield was only 59.4% [45b]. Better




$ArNH_2$ = NDA or mono-carbamate of NDA

**Scheme 17.**

results have been recently obtained with zirconia supported over $SiO_2$ [45c]. Under optimal reaction conditions ($ZrO_2$ load = 1 wt %; 443 K; 7 h; DMC/aniline = 20 mol/mol; catalyst/aniline = 25 wt %), conversion of aniline was 98.6 % and PhNHC(O)OMe yield 79.8 %.

To date, the highest activities, among the metal oxides investigated as catalysts for methoxycarbonylation of aniline, have been exhibited by yellow and red PbO [44a]. In the presence of red PbO, aniline conversion and carbamate selectivity as high as 98 % were achieved after 1 h at 433 K. Actually, also a few other lead compounds ($Pb_3O_4$, $PbCO_3$, $Pb_3(CO_3)_2(OH)_2$, $Pb(O_2CCH_3)_2{\cdot}Pb(OH)_2$) have been shown to be active and selective catalysts for the synthesis of methyl *N*-phenyl carbamate from aniline and DMC [44a].

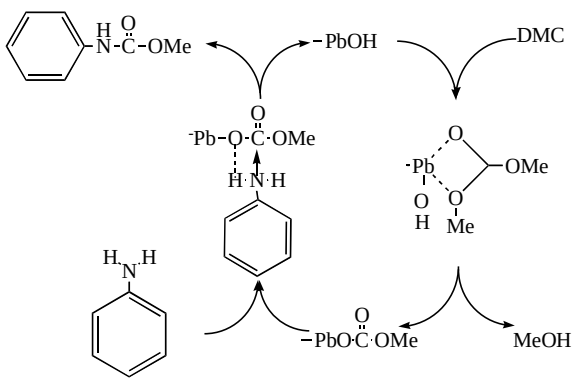
Kinetic experiments carried out with orthorhombic PbO (yellow) showed the existence of an induction time, which disappeared by treating PbO with DMC or methanol. These results indicated that PbO was not the real catalyst, but merely a precursor of the catalytically active species. XRD analysis showed that, upon pretreatment with DMC, PbO converted into $3PbO{\cdot}H_2O$. Similarly, upon pretreatment of PbO with methanol, new phases, due to $Pb(OMe)_2$ and $3PbO{\cdot}H_2O$, were found. The disappearance of the induction time upon treating PbO with DMC or methanol and the formation of $Pb(OMe)_2$ and/or $3PbO{\cdot}H_2O$ have suggested that hydroxyl or methoxy groups attached to Pb may play a key role in the catalytic process. On these bases, the mechanism summarized in Scheme **18** has been proposed, although no evidence for DMC coordination to Pb(II) has been ever presented so far.

As for Pb-based catalysts, particular attention has received lead acetate. At 453 K, $Pb(O_2CCH_3)_2{\cdot}3H_2O$ catalyzed the formation of (**1b**) from MDA and DMC, albeit not so effectively as $Zn(O_2CCH_3)_2{\cdot}2H_2O$ [43c]. In a more recent study, anhydrous $Pb(O_2CCH_3)_2$ has been successfully used as catalyst for the synthesis of (**2b**) from TDA and DMC [44d]. At 443 K, using a DMC/TDA molar ratio of 20 and a TDA/$Pb(O_2CCH_3)_2$ molar ratio of 50, the diamine was quantitatively (100 %) converted into the diester (**2b**) with 97.7 % selectivity within 4 h. XRD measurements on the catalyst recovered after reaction showed that, during the catalytic run, $Pb(O_2CCH_3)_2$ converted into $Pb_3(CO_3)_2(OH)_2$ upon reaction with DMC and co-formed methanol (eq. **23**). The reaction also produced methyl acetate, which was detected in the reaction mixture. Remarkably, $Pb(O_2CCH_3)_2$ can be regenerated from the recovered catalyst, by treating $Pb_3(CO_3)_2(OH)_2$ with acetic acid, at ambient temperature.

$$3\,Pb(O_2CCH_3)_2 + 3\,CH_3OH + 2\,(CH_3O)_2CO \longrightarrow Pb_3(CO_3)_2(OH)_2 + 6\,CH_3C(O)OCH_3 \quad \textbf{(23)}$$

Pb(II) salts are also active catalysts for carbonylation and carbonylation/methylation of *o*-phenylenediamine and *o*-aminophenol with dimethyl carbonate [44b]. 2-Benzimidazolone was obtained in 84 % yield by reacting *o*-phenylenediamine with DMC for 1 h at 443 K in the presence of $Pb(NO_3)_2$. At 473 K, in the presence of $Pb(O_2CCH_3)_2$, the reaction gave quantitatively 1,3-dimethyl-2-benzimidazolone, which formed by double methylation of the primary product, 2-benzimidazolone. In the presence of $Pb(O_2CCH_3)_2$, the reaction of *o*-aminophenol with DMC afforded selectively, depending on the reaction conditions, the carbonylation product 2-benzoxazolone or the carbonylation/methylation product 3-methyl-2-benzoxazolone.

A few lead compounds are also effective catalysts for methoxycarbonylation of aliphatic amines $RNH_2$ (R = *n*-hexyl, *n*-butyl, *n*-propyl) with DMC [44c]. Among the Pb compounds investigated, $Pb(NO_3)_2$ was the most effective catalyst, while PbO and $PbCO_3$, which were active catalysts for methoxycarbonylation of aniline, showed, in this case, a low catalytic activity. Under solvent free conditions, $Pb(O_2CCH_3)_2$ efficiently promoted the methoxycarbonylation of *n*-hexylamine [44c], but was a much poorer and less selective catalyst for carbamation of 1,6-diaminohexane [42]. In methanol as solvent, bis-methoxycarbonylation of 1,6-diaminohexane with DMC was more effectively catalyzed by $Bi(NO_3)_3$. Carbamate formation was accompanied by side-production of variable amounts of *N*-methylated derivatives and ureas [42]. After 18 h at 353 K, diamine conversion was quantitative, while mono and dicarbamate GC-yields were as high as 11 and 84 %, respectively.




**Scheme 18.**

Attention has been devoted also to explore the catalytic activity of RE and Group 3 metal salts [46]. In principle, these systems are more friendly to environment, as they offer lower toxicity than other known carbamation catalysts.

A brief report has described a facile synthesis of carbamates from aliphatic or aromatic amines and DMC, at 353 K, using hydrate $Yb(OTf)_3$ (5 mol % *vs* amine; DMC/amine = 5 mol/mol)) as catalyst [46a]. At 343 K, yttrium acetate and several other RE (Yb, Eu, Gd, Tb, Dy, Ho, Er, Tm, Lu) compounds have been claimed to be active as catalysts for alkoxycarbonylation of aliphatic, cycloaliphatic, araliphatic amines with dialkyl carbonates [46c,d]. In another patent, $Nd(O_2CNH(i\text{-}C_3H_7))_3$ and $Pr(O_2CNH(i\text{-}C_3H_7))_3$ were reported to catalyze effectively, in the range 413-453 K, the methoxycarbonylation of aromatic amines (aniline, TDA) with DMC [46b].

Recently, the catalytic activity of Group 3 metal salts, such as anhydrous $Sc(OTf)_3$ and $La(OTf)_3$, has been matter of a few detailed studies [24,46e-g].

At ambient temperature (293 K), scandium triflate can promote effectively the methoxycarbonylation of aliphatic primary and secondary amines (benzyl-, allyl-, *n*-butyl-amine, morpholine, piperidine) with DMC (DMC/amine = 2.33 – 2.91 mol/mol; Sc/amine = 3 mol %) in good yields (≥ 80 %, isolated) and with excellent selectivities (≈ 100 %) [46e]. Lanthanum triflate was also a very effective catalyst, but less active than the scandium salt [46e].

At 293 K, $Sc(OTf)_3$ catalyzed selectively (≈ 100 %) also the bis-methoxycarbonylation of aliphatic diamines (DMC/diamine: 2.4 – 3.0 mol/mol; Sc/$NH_2$ group = 1.5 mol%) such as 1,3-diaminopropane, 1,4-diaminobutane and industrially more relevant 1,6-diaminohexane, *meta*-xylylenediamine and *para*-xylylenediamine [46f]. The corresponding dicarbamates were isolated as pure compounds in yields ≥ 80 %.

Under conditions analogous to those used for aliphatic amines, aromatic amines did not react with DMC. At 363-368 K, in the presence of the anhydrous $M(OTf)_3$ salts (M = Sc, La), aniline reacted with DMC to give mainly *N*-methylation products (PhN(Me)H and $PhNMe_2$) [24]. Nevertheless, both the $M(OTf)_3$ salts (M = Sc, La) were effective catalysts for methoxycarbonylation of aromatic amines (aniline, MDA, TDA) with MPC [24].

**Table 1. Methoxycarbonylation of $PhCH_2NH_2$ with DMC in the Presence of $M(OTf)_3$ (M = La, Sc) at 293 K: Influence of $H_2O$ on the Catalytic Activity[a]**

| Entry | Metal Salt | M (La, Sc) (mmol) | Time (h) | Carbamate (%)[b] |
|---|---|---|---|---|
| 1 | $La(OTf)_3$ | 0.067 | 24.0 | 71 |
| 2 | $La(OTf)_3/H_2O$[c] | 0.065 | 9.5 | 7 |
| 3 | $Sc(OTf)_3$ | 0.072 | 20.9 | 75 |
| 4 | $Sc(OTf)_3/H_2O$[d] | 0.079 | 24 | 10 |

[a] $PhCH_2NH_2$: 0.100 mL, 0.916 mmol; DMC: 1.0 mL, 11.87 mmol (in all the runs). [b]GC yield *vs* the amine [c]Added $H_2O$: 8 μL; mol $H_2O$/mol La = 7:1.[d]Added $H_2O$: 8.5 μL; mol $H_2O$/mol Sc = 6:1.

In general, rising temperature affected negatively carbamate selectivity because of incidence of *N*-methylation processes. Moreover, the methoxycarbonylation reaction required strictly anhydrous conditions. Addition of water to the reaction mixture markedly inhibited the catalytic activity of both triflate salts (Table **1**) and caused the precipitation of poorly soluble metal-carbamato-species, which, under the working conditions, showed no or very poor catalytic activity. The starting catalyst, $M(OTf)_3$ (M = Sc, La), modified during the catalytic process, as, in the presence of amine, it underwent OMe/OTf exchange by reaction with coproduced methanol (eq. **1**; R" = Me) and converted into catalytically less active M-methoxo species (eqs. **24a** and **24b**).

$$L_nM(OTf)_3 + x\ MeOH + x\ RR'NH \longrightarrow L_nM(OMe)_x(OTf)_{3-x} + x\ (RR'NH_2)OTf \quad \textbf{(24a)}$$

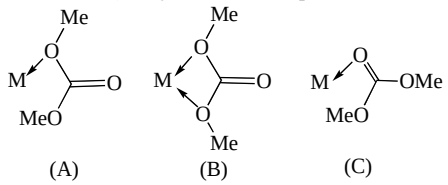
M = Sc, La ; L = ligand, R' = H, alkyl

$$L_nM(OTf)_3 + x\ MeOH + x\ MeO(O)CNH\text{-}R\text{-}NH_2 \longrightarrow L_nM(OMe)_x(OTf)_{3-x} + x\ (MeO(O)CNH\text{-}R\text{-}NH_3)OTf \quad \textbf{(24b)}$$

M = Sc ; L = ligand, R = $(CH_2)_n$ (n = 3, 4, 6); *m*-$CH_2$-$C_6H_4$-$CH_2$; *p*-$CH_2$-$C_6H_4$-$CH_2$

As for metal catalysis, activation of organic carbonate by coordination to the metal centre has been often invoked, but in most cases without the support of any experimental evidence. Indeed, the coordinating properties of organic carbonates towards metal centres have been documented only in a few studies and for a very limited number of metal ions.

$^{13}C$ NMR resonances of several organic carbonates undergo an appreciable shift in solutions containing Li salts ($LiPF_6$, $LiBF_4$, etc) [47]. The $^{13}C$ shifts observed are positive both for the carbonyl carbon and the carbon atoms adjacent to the ester oxygens of the carbonate moiety, as, for instance, are the methyl carbons of DMC. The shifts measured in the presence of the electrolyte have been attributed mainly to coordination of organic carbonate to $Li^+$ through the carbonyl oxygen (see (C) in Scheme **19**), although conformational changes during coordination or some direct contribution of coordination modes involving the ester O-atoms (see (A) and (B) in Scheme **19**) may also have importance [47].




**Scheme 19.** Coordination modes of DMC.

Recently, Zecchina *et al.* [48] have considered the binding properties of DMC towards $Na^+$ cations to explain the IR spectrum of DMC in the restricted spaces of supercages of NaY zeolites. Theoretical calculations supported the formation of both (B)- and (C)-like adducts (Scheme **19**, M = $Na^+$). Both experimental and calculated spectra indicated that $\nu$(C=O) and $\nu_{asymm}$(OCO) modes were, respectively, blue- and red-shifted with respect to free $DMC_{(g)}$ in the (B)-like adduct (M = $Na^+$; $\nu$(C=O) = 1772 $cm^{-1}$, $\nu_{asymm}$(OCO) = 1284 $cm^{-1}$), while underwent an opposite shift in the (C)-like DMC-$Na^+$ species [$\nu$(C=O): to red (1747 $cm^{-1}$); $\nu_{asymm}$ (OCO): to blue (1311 $cm^{-1}$)]. Unfortunately, the IR spectra did not provide any data for the shifts of $\nu_{asymm/symm}(OCH_3)$ modes, whose absorptions fell within the zeolite framework region.

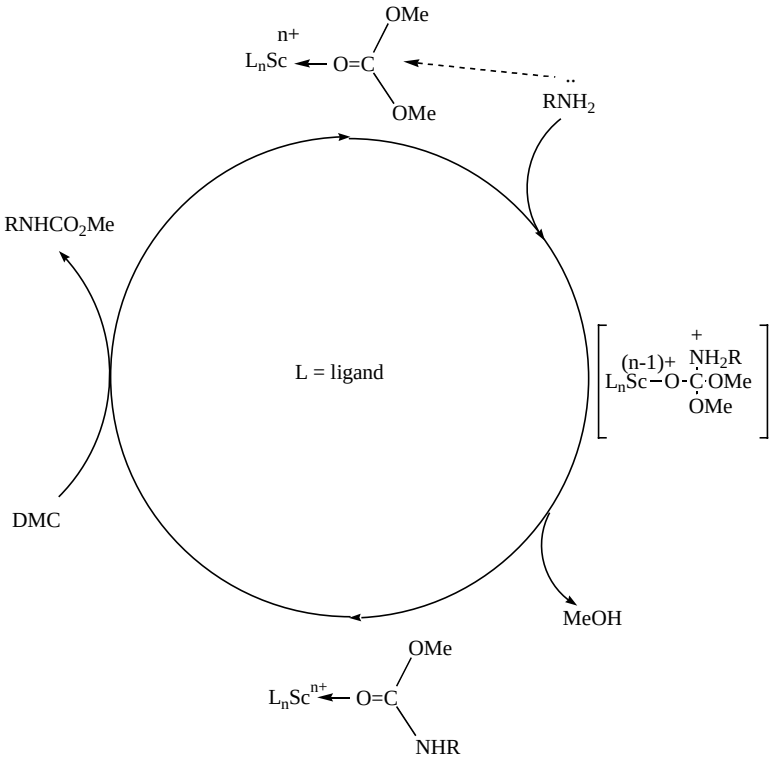
As already discussed, gaseous DMC does not coordinate to anhydrous zinc acetate in the temperature range 293 – 453 K [43f]. However, it has been argued that, in solution, MeOH can promote the coordination of DMC to zinc ion with formation of a $\eta^1$-O(C=O) DMC-Zn(II) adduct (see above Scheme **16**) [43e].

Recently, the ability of DMC to coordinate to Sc(III) has been fully demonstrated by Quaranta et al. by isolating, for the first time, a DMC-metal complex characterized as ($\eta^1$-O(C=O)-DMC)$Sc(OTf)_3$ [46g]. The negative shift for the C=O stretching vibration ($\Delta\nu$(C=O) = - 121 $cm^{-1}$) excluded coordination modes like (A) or (B) (Scheme **19**), for which a positive shift ($\Delta\nu$(C=O) > 0) should be expected, and indicated that DMC was coordinated to the metal centre through the O-carbonyl atom (see (C), Scheme **19**) [49-51]. $\eta^1$-O(C=O) Coordination of the organic carbonate to the metal centre shifts to red not only $\nu$(C=O), but also both asymmetric and symmetric $CH_3$-O stretching frequencies. Unfortunately, the absorptions due to the asymmetric and symmetric $\nu$(OCO) vibrations could not be located exactly, as these bands were masked by the strong absorptions due to OTf groups.

In solution, the ability of DMC to coordinate $Sc(OTf)_3$ is strongly affected by the nature of solvent [46g]. DMC easily coordinates to Sc(III) in a non coordinating solvent such as $CH_2Cl_2$ and in $CH_3CN$ solution. However, the coordinating properties of DMC towards $Sc(OTf)_3$ decrease somewhat in an *O*-donor solvent like THF, and no evidence of DMC coordination to $Sc(OTf)_3$ has been found in solvents as MeOH or $H_2O$.

An IR study of the system $Sc(OTf)_3/PhCH_2NH_2$/DMC, at ambient temperature, has shown that the catalytic formation of carbamate ester (Eq. (**1**); R' = Me, cat. = $Sc(OTf)_3$) is promoted by the coordination of DMC to the metal centre, and has demonstrated the key role played by scandium(III) in activating the substrate (DMC) even in the presence of potentially coordinating *N*-donor species (mono and diamines), at least when the methoxycarbonylation reaction is carried out under the most usual conditions which employ an excess of DMC with respect to amine [46g]. Scheme **20** summarizes a reasonable reaction scheme for the $Sc(OTf)_3$-catalyzed methoxycarbonylation of aliphatic amines with DMC.

Differently from $Zn(O_2CCH_3)_2{\cdot}2H_2O$ [43e], coordination of DMC to $Sc(OTf)_3$ is not assisted by any promoter, and the presence of *O*-donors (methanol, THF, $H_2O$) restrains significantly the catalytic activity of the triflate salt (Table **1** and Fig. (**2**)). *O*-donors, competing effectively with DMC for the coordination sites of metal centre, hamper the coordination of the organic carbonate to Sc(III). The inhibitory effect is more pronounced in the presence of MeOH (curve (c), Fig. (**2**)) or water (Table **1**), which are not only *O*-




**Scheme 20.** Catalytic methoxycarbonylation of aliphatic amines with DMC promoted by $Sc(OTf)_3$.

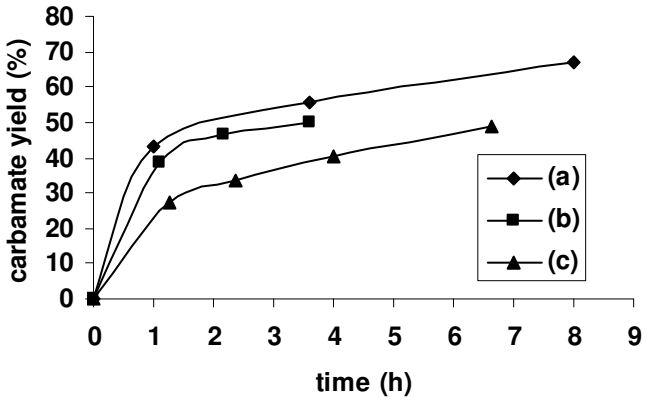



**Fig. (2).** Influence of *O*-donor species on the methoxycarbonylation of $PhCH_2NH_2$ with DMC in the presence of $Sc(OTf)_3$ (293 K). (**a**) No *O*-donor was used. Sc/amine/DMC: 1/12.3/176 mol/mol; (**b**) *O*-donor: THF. Sc/amine/THF/DMC: 1/12.3/12.6/176 mol/mol; (**c**) *O*-donor: MeOH. Sc/amine/MeOH/DMC: 1/12.3/ 12.6/176 mol/mol.

donors, but also protic species, and can bring about the modification of the starting catalyst with generation of catalytically less active species (see above).

The interaction of the organic carbonate with Sc(III) perturbs DMC molecule markedly and weakens not only the C=O bond of DMC ($\Delta\nu$(C=O) < 0), but also the O-$CH_3$ bonds of the organic carbonate, as supported by the negative shifts ($\Delta\nu$ = -35 and -33 $cm^{-1}$, respectively) measured for $\nu_{asymm}$(O-$CH_3$) and $\nu_{symm}$(O-$CH_3$) modes of (DMC)$Sc(OTf)_3$. Therefore, $\eta^1$-O(C=O) coordination of DMC to Sc(III) activates both the carbonyl group and the O-$CH_3$ moieties [46g]. This provides a rationale not only for the enhancement of the methoxycarbonylating reactivity of the carbonate when reacted with aliphatic amines (Table **2**, entries 1 and 2), but also accounts for the enhanced methylating reactivity of DMC in the reaction with a less hard aromatic amine, such as aniline (Table **2**, entries 3 and 4).

## 4. CONCLUSIONS

Carbonylation of amines with carbonic acid diesters is a practicable synthetic way to carbamates and offers a new solution to the synthesis of carbamates and other classes of compounds, such as isocyanates and ureas, through a route which avoids phosgene and $COCl_2$- derivatives.

The studies in this field mark an important contribution to the development of a safer and greener chemistry which may replace

**Table 2. Reactions of $PhCH_2NH_2$ and $PhNH_2$ with DMC at 363 K: Catalytic Effect of $Sc(OTf)_3$**

| Entry | R | $RNH_2$ (mmol) | DMC (mmol) | $Sc(OTf)_3$ (mmol) | Time (h) | Yield (%)[a] (%) | |
|---|---|---|---|---|---|---|---|
| | | | | | | RNHC(O)OMe | R(Me)NH + $RNMe_2$ |
| 1 | $PhCH_2$ | 18.3 | 237 | - | 24 | 13 | 3.5 |
| 2 | $PhCH_2$ | 0.92 | 11.9 | 0.0737 | 1 | 60 | < 1 |
| 3 | Ph | 1 | 10.8 | - | 96 | - | < 2 |
| 4 | Ph | 0.82 | 9.03 | 0.0527 | 24 | 8 | 35 |

[a] GC-yield *vs* $RNH_2$.

conventional processes based on phosgenations reactions. Carbonic acid diesters, DMC *in primis*, can play a key role in this context. Accordingly, the search for new phosgene-free methods of synthesis of DMC and other organic carbonates is under continuous evolution, as the recent progresses achieved in the synthesis of carbonates by carboxylation of alcohols (eq. **25**) clearly demonstrate [52].

$$2\ ROH + CO_2 \xrightarrow{\text{Cat.}} (RO)_2CO + H_2O \qquad \textbf{(25)}$$

The review emphasizes that, under proper conditions, even unactivated carbonates can be used as carbonylating agents for a variety of aliphatic and aromatic amines. The fervid research activity in this area is in rapid expansion and is quickly extending to substrates other than amines, as shown by a few very recent studies describing the use of carbonic acid diesters (DMC, DPC, MPC, dibenzyl carbonate, butyl phenyl carbonate), as reagents for *N*-carbonylation of *N*-heteroaromatic compounds, such as pyrrole, indole, carbazole [53].

The great effort devoted to search for effective and selective carbonylation catalysts is far to be considered concluded. For the studied processes be practical on an industrial scale, new catalysts will have to be developed. The search for more eco-friendly reusable catalysts, characterized by high selectivity and efficiency (high TON/TOF) under as much as possible mild reaction conditions is still a major task in this field. Understanding the factors which affect the efficiency and selectivity of reacting system is of primary importance, and a significant contribution to their characterization may come from studying more thoroughly the molecular aspects of catalysis.

## ACKNOWLEDGEMNTS

Authors thank Università di Bari (Fondi di Ateneo) and MiUR (PRIN 2006031888_001) for funding.

## ABBREVIATIONS

| | | |
|---|---|---|
| Alloc | = | allyloxycarbonyl |
| ADP | = | adenosine 5'-diphosphate |
| ATP | = | adenosine 5'-triphosphate |
| BMIm | = | 1-butyl-3-methyl imidazolium |
| Boc | = | *t*-butoxycarbonyl |
| BuPy | = | 1-butyl-pyridinium |
| CAL | = | *Candida Antartica* lipase |
| Cbz | = | benzyloxycarbonyl |
| CP | = | $^-O_2COPO_3^{2-}$, carboxyphosphate |
| CPS | = | carbamoyl phosphate synthetase |
| DEC | = | diethyl carbonate |
| DMAP | = | (4-*N*,*N*-dimethylamino)pyridine |
| DMC | = | dimethyl carbonate |
| DPC | = | diphenyl carbonate |
| e.e. | = | enantiomeric excess |
| HSAB | = | hard and soft acid-base (Pearson's theory) |
| IL | = | ionic liquid |
| MDA | = | 4,4'-methylenedianiline |
| MPC | = | methyl phenyl carbonate |
| NDA | = | 1,5-diaminonaphtalene |
| NDC | = | 1,5-naphtalene dicarbamate dimethyl ester |
| N-Mim | = | *N*-methylimidazole |
| OTf | = | triflate |
| RE | = | rare earths |
| RMIm | = | 1-alkyl-3-methyl imidazolium |
| SET | = | selective energy transfer |
| TBD | = | 1,5,7-triazabicyclo[4.4.0]dec-ene |
| TDA | = | 2,4-diaminotoluene |
| XRD | = | X-ray diffraction |

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Received: June 25, 2008 Revised: September 23, 2008 Accepted: November 06, 2008